

### **Remarks**

Claims 1-24 are pending in the present application. Claims 1-13 are rejected under 35 USC §112. Claims 1, 6-7 and 9-24 are rejected under 35 USC §103(a). Claims 14-24 are rejected under the judicially created doctrine of obviousness-type double patenting. Applicants respectfully request reconsideration of the application, withdrawal of all rejections, and allowance of the application in view of the amendments and remarks below.

### **The Invention**

The present invention provides novel condensation aerosols comprising erectile dysfunction drugs and methods for producing such aerosols. These condensation aerosols have little or no pyrolysis degradation products. The unique method for generating or producing such aerosols employs rapid vaporization of a composition of an erectile dysfunction drug to minimize drug degradation during the process. The vaporized drugs are subsequently condensed to form particles of a desirable particle size for inhalation. These aerosols are especially useful in the treatment of acute or chronic conditions wherein rapid onset of treatment is desirable.

### **The Amendments to the Claims**

Without prejudice to the Applicants' rights to present claims of equal scope in a timely filed continuing application, to expedite prosecution and issuance of the application, the Applicants have amended Claims 1-3, 5, 11-14, 16 and 18-23 and cancelled Claims 4, 7-10, 15 and 17. The Applicants also have presented new Claims 25-47. The amended claims and the new claims are supported by the specification (see below for examples of such support).

<b>Claim</b>	<b>Examples of Support in the Specification</b>
Claim 1	Paragraphs 0005, 0009, 0013, 0015, 0016, 0018; Examples 2-3
Claim 2	Paragraphs 0013, 0025, 0034, 0046
Claim 3	Paragraphs 0039, 0057
Claim 5	Paragraphs 0038, 0053
Claim 11	Paragraph 0054
Claim 12	Paragraph 0055
Claim 13	Paragraph 0056
Claim 14	Paragraphs 0005, 0009, 0013, 0015, 0016, 0018; Examples 2-3
Claim 16	Paragraphs 0005, 0009, 0013, 0015, 0060-0061

Claim 18	Paragraphs 0005, 0009, 0013, 0015, 0060-0061, 0095-0096; Examples 2-3 and Figure 1
Claim 19	Paragraph 0094
Claim 20	Paragraph 0094
Claim 21	Paragraph 0094
Claim 22	Paragraph 0090; Examples 2-3
Claim 23	Paragraphs 0039, 0057
Claim 25	Paragraphs 0001 [incorporates by reference U.S. provisional application Ser. No. 60/317,479 (see, e.g., page 30, lines 25-27)], 0012, 0026, 0035, 0047
Claim 26	Paragraphs 0001 [incorporates by reference U.S. provisional application Ser. No. 60/317,479 (see, e.g., page 30, lines 25-27)], 0012, 0026, 0035, 0047
Claim 27	Paragraphs 0006, 0016, 0029, 0041
Claim 28	Paragraphs 0006, 0016, 0029, 0041
Claim 29	Paragraphs 0028, 0040; Examples 2-3
Claim 30	Paragraphs 0028, 0040; Examples 2-3
Claim 31	Paragraphs 0016, 0054
Claim 32	Paragraphs 0016, 0055
Claim 33	Paragraphs 0016, 0056
Claim 34	Paragraphs 0013, 0015, 0034, 0046
Claim 35	Paragraphs 0001 [incorporates by reference U.S. provisional application Ser. No. 60/317,479 (see, e.g., page 30, lines 25-27)], 0012, 0026, 0035, 0047
Claim 36	Paragraphs 0001 [incorporates by reference U.S. provisional application Ser. No. 60/317,479 (see, e.g., page 30, lines 25-27)], 0012, 0026, 0035, 0047
Claim 37	Paragraphs 0006, 0016, 0029, 0041
Claim 38	Paragraphs 0006, 0016, 0029, 0041
Claim 39	Paragraphs 0028, 0040; Examples 2-3
Claim 40	Paragraphs 0028, 0040; Examples 2-3
Claim 41	Paragraphs 0016, 0054
Claim 42	Paragraphs 0016, 0055
Claim 43	Paragraphs 0016, 0056
Claim 44	Paragraph 0090
Claim 45	Paragraph 0090
Claim 46	Paragraph 0093
Claim 47	Paragraph 0091

The amendments to the claims do not introduce new matter. Applicants respectfully submit that the amendments to the claims put the case in condition for allowance. The Examiner is respectfully requested to enter the amendments to the claims and allow all amended claims.

### **The Rejection under 35 U.S.C. §112**

The Examiner rejected Claims 1-13 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the phrase “by the patient of the formation of, and delivery of, the condensation aerosol” in Claims 1 and 7 was found to be unclear and redundant. Claim 1 has been amended to eliminate this phrase. Claim 7 has been cancelled.

### **The Rejection under 35 U.S.C. §103(a)**

The Examiner rejected Claims 1, 6, 14, 16 and 18-24 under 35 U.S.C. §103(a) as being unpatentable over Bartus et al. (6,514,482) in view of Faithfull et al. (6,041,777). In support of this rejection, the Office Action states that “Bartus teaches a method of pulmonary delivery of a medicament, which includes administering . . . particles . . . , where the particles preferably have an aerodynamic diameter between about 1 and 5  $\mu\text{m}$ .” Office Action at 2-3. The Office Action further states that Bartus discloses medicaments containing from 1 to about 90 weight percent of drugs, including apomorphine, that are delivered via a dry powder inhaler, metered dose inhaler, nebulizer or instillation techniques. *Id.* at 3.

The Office Action states that Bartus lacks “teachings on producing condensation aerosol and also lacks specific disclosure on the presence of less than 5% degradation products.” *Id.* at 3. The Office Action states in summary that Faithfull teaches methods and apparatus for closed-circuit ventilation therapy, including the use of nebulizers to provide fluorochemicals and/or pharmaceutical agents, heated above body temperature, to a ventilating gas in the form of a vapor and that this is accomplished by spraying or contacting a wetted surface or wick with the gas to form droplets. *Id.* at 3-4.

The Office Action states that it “would have been obvious to a person of ordinary skill in the art at the time the invention was made to have modified the method of delivering a medicament to a patient’s respiratory tract of Bartus, by adding the steps of heating the composition and having patient inhale the condensates, because of the disclosed benefits of such a method, including minimized trauma to the lungs and a better resolution of pulmonary and systemic disorders, as taught by Faithfull.” *Id.* at 4.

Applicants respectfully disagree in view of the elements of the pending claims and the disclosures of Bartus and Faithfull. Bartus fails to teach or disclose a condensation aerosol. Rather Bartus is directed to a method of delivering low tap density particles for the treatment of CNS disorders and in particular, Parkinson’s disease, via dry power inhalers or metered dose inhalers. Nowhere does

Bartus disclose or suggest an aerosol particle formed as a condensate of a vaporized drug, nor the advantages obtained by such a condensate aerosol. Additionally, Bartus lacks teachings on heating the composition. Dry powder inhalers, metered dose inhalers, nebulizers or instillation techniques do not vaporize the drug and then form a condensate of the drug. Additionally, in Bartus there is no disclosure of how one would form such particles of an antiparkinsonian drug or any other drug compound with less than 10% drug degradation products, or how to obtain aerosols having a MMAD of less than 5 microns when vaporizing the drug. Nor does Bartus disclose heating a thin layer, containing the drug, on a solid support. These elements, which are not taught in Bartus, are required by Claims 1, 14 and 16.

Faithfull does not cure these deficiencies or make obvious in view of Bartus how to accomplish these tasks. Faithfull does not disclose or teach a condensation particle or aerosol as defined by the Applicants' claims or how to make such an aerosol. Faithfull discloses the use of a warmed fluorochemical as a solvent for delivering the active compound "oxygen" to the lungs of the patient using a ventilation system. The active or therapeutic compound or drug in Faithfull is not vaporized and subsequently condensed into aerosol particles, as is set forth in Claims 1, 14 and 16 of the present application. Moreover, there is no teaching in Faithfull of drawing air through an enclosure being effective to condense a vapor to form a condensation aerosol, as required in Claim 19. Rather, Faithfull teaches away from such a condensation particle, as oxygen gas is already being passed through the system described by Faithfull and no condensation particle is formed. Instead, Faithfull requires the use of a wetted surface or wick to get the fluorochemical (solvent) to form a droplet. Moreover, as is stated in the Office Action, the fluorochemical in the Faithfull reference, unlike the present invention, is being delivered to the lung as a vapor and not an aerosol. See Office Action at 4 ("As the fluorochemical **vapor** cools in the body it is deposited on the pulmonary surfaces" (emphasis added)). Faithfull does not disclose how to make a condensation aerosol, how to obtain condensation particles with the purity disclosed in the present application, or how to obtain MMAD sizes of less than 5 microns for condensation aerosols. Nor does Faithfull disclose heating a thin layer, containing the drug, on a solid support.

The Office Action suggests that condensates by their nature have a high percentage of purity of the drug and less degradation products. Applicants respectfully disagree. The mere fact that an aerosol is formed by condensation does not mean that the aerosol will have a high percentage of drug and less degradation products.

According to the MPEP § 2143, "to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art references (or references when combined) must teach or suggest all the claim limitations." Obviousness cannot be established by combining teachings in the prior art, absent some teaching or suggestion in the prior art that the combination be made (*In re Stencel* 828 F. 2d 751, 4 USPQ2d 1071 (Fed. Cir. 1987); *In re Newell* 891 F. 2d 899, 13 USPQ2d 1248 (Fed. Cir. 1989)).

Faithfull does not cure the deficiencies of Bartus. Accordingly, the Office Action fails to establish even a *prima facie* case of obviousness as each and every element of the invention is not taught or disclosed by these references. Moreover for the same reason, there would be no motivation to combine the references to achieve the presently claimed invention. Even if Bartus and Faithfull were combined, the claimed invention would not result because neither Bartus nor Faithfull is directed to heating a thin layer containing a drug, on a solid support, or to forming condensation aerosols suitable for inhalation that are characterized by less than 10% drug degradation products and an MMAD of less than 5 microns.

Claims 2, 3, 5, 6, 11-13, and 25-34 which depend from Claim 1 patentably define over Bartus and Faithfull for the same reasons as Claim 1. Claims 18-24 and 35-47 which depend from Claim 16 patentably define over Bartus and Faithfull for the same reasons as Claim 12.

Finally, the Examiner rejected Claims 1, 6-7 and 9-24 under 35 U.S.C. 103(a) as being unpatentable over Bartus et al. (6,244,334) in view of Byron et al. (20040016427 A1) and Wilson et al. (20020037828 A1). Office Action at 4. The Office Action states that Bartus "lacks disclosure on condensation aerosols and the devices for producing condensates involved in the method of therapy," but that "Byron et al. disclose a method and apparatus for generating an aerosol . . . formed by supplying a material in liquid form to a tube and heating the tube such that the material volatilizes and expands out of an open end of the tube." *Id.* at 4-5. The Office Action goes on to state that the volatilized material combines with ambient air such that volatilized material condenses to form the aerosol and that the aerosols are intended for inhalation and typically have a mass median particle diameter of less than 2 microns. Thus according to the Office Action, it would have been obvious to take the device of Byron and use it to deliver the aerosolized composition of Bartus to a subject's respiratory tract as it would be desirable to provide an aerosol delivery article capable of making small particles without exposure to significant heat or high temperatures. *Id.*

Applicants respectfully disagree. One of skill in the art seeking to prepare and administer aerosolized compositions for delivery to a subject's respiratory tract without exposure to significant heating or high temperatures would not have to look beyond the disclosure of Bartus. Moreover, Bartus does not teach that small particles are desirable. To the contrary, Bartus states that larger, low density particles aerosolize more efficiently and avoid phagocytic engulfment by alveolar macrophages more effectively than smaller, denser aerosol particles. Bartus col. 13, lines 61-64.

"The aerodynamic diameter can be calculated to provide for maximum deposition within the lungs. Previously this was achieved by the use of very small particles of less than about five microns in diameter, preferably between about one to about three microns, which are then subject to phagocytosis. Selection of particles which have a larger diameter, but which are sufficiently light (hence the characterization "aerodynamically light"), results in an equivalent delivery to the lungs, but the larger size particles are not phagocytosed. Improved delivery can be obtained by using particles with a rough or uneven surface relative to those with a smooth surface" (Bartus col. 13, line 65 to col. 14, line 7).

As pointed out in the Office Action, the aerosols generated by the device of Byron typically have a mass median particle diameter of less than 2 microns, while Bartus teaches that the preferred size range of particles is at least about 5 microns, preferably between about 5 microns and 30 microns. See, e.g., Bartus at col. 12, lines 60-66; col. 14, lines 12-14. Thus, Bartus teaches away from delivering its compositions using the device of Byron et al.

Moreover, one of skill in the art would not have a reasonable expectation that the device of Byron et al. would successfully form condensation aerosols suitable for inhalation that are characterized by less than 10% drug degradation products and an MMAD of less than 5 microns. For instance, under the method of Byron et al., the compositions of Bartus ("solid component") would have to be put into liquid form by combining with a "liquid component." Byron et al., paragraph 0076. However, Byron et al. fails to provide specific guidelines for selecting an appropriate "liquid component" for a given drug ("solid component") or for predicting what effect heating the mixture will have on the solid component. This is further complicated when the solid component contains one or more additional component in addition to the drug, such as the surfactants, phospholipids, amino acids, etc., taught in Bartus. Bartus, col. 8, lines 42 to col. 11, line 53.

Finally, neither these references do not teach or suggest all of the elements of Claims 1, 14 and 16. Like Bartus, Byron et al. lacks specific disclosure on the presence of less than 10% degradation

products. Furthermore, neither Byron nor Bartus describe heating a thin layer, containing the drug, on a solid support.

The Office Action states that Bartus does not specifically disclose sildenafil, tadalafil, or vardenafil, but that Wilson et al. teaches compositions and a method for treatment of premature ejaculation by administering a phosphodiesterase inhibitor, such as sildenafil, vardenafil, zaprinast, including administration via inhalation. *Id.* at 5. The Office Action goes on to state that it would be obvious to one of skill in the art to look in the art for other suitable active agents that can be used with the “system of delivery” discussed above (i.e., using the device of Byron to deliver the composition of Bartus). *Id.* at 5.

Applicants respectfully disagree in view of the amended claims and the disclosures of Wilson. As noted above, Bartus and Byron et al. do not teach the elements of Claims 1, 14 and 16, but rather teach away from the claimed invention. Wilson et al. does not cure these deficiencies or make obvious in view of Bartus and Byron et al. how to accomplish these tasks. Bartus not only fails to disclose the compounds recited in Claims 1, 14 and 16, it also fails to disclose heating the composition. Wilson et al. does not disclose or teach a condensation aerosol as defined by the present claims or how to make such an aerosol. Wilson at most mentions that “suitable compositions and dosage form include . . . dry powder or aerosolize formulation for inhalation.” See US 2002/0037827 A1, paragraph 0074. Wilson also does not disclose heating of the composition, nor does Wilson disclose how to generate a condensation aerosol characterized by less than 10% drug degradation products and an MMAD of less than 5 microns. Furthermore, Wilson et al. does not describe heating a thin layer, containing the drug, on a solid support.

Thus, these references singly or in combination do not teach or suggest all the claim elements, but rather teach away from the claimed invention. Accordingly, the Office Action fails to establish even a *prima facie* case of obviousness. Moreover for the same reason, there would be no motivation to combine the references to achieve the presently claimed invention, nor is it seen how the combination of the references would achieve the presently claimed invention. Claims 2, 3, 5, 6, 11-13, and 25-34 which depend from Claim 1 are not obvious for the same reasons as Claim 1. Claims 18-24 and 35-47 which depend from Claim 16 are not obvious for the same reasons as Claim 12.

Accordingly, and in light of the foregoing arguments, the Applicants respectfully submit that these amendments put the case in condition for allowance and request that the Examiner reconsider and withdraw all rejections based on 35 U.S.C §103.

### **Double Patenting**

Claims 14-24 were rejected under the judicially created doctrine of obviousness-type double patent as being unpatentable over claims of U.S. Patent No. 6,803,031 B2, as these claims are "either anticipated by, or would have been obvious over, the reference claims." Office Action at 6. Also, Claims 16-24 were provisionally rejected under the doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of copending Application No. 10/769,197. *Id.*

Applicants have filed with this response Terminal Disclaimers with regard to U.S. Patent No. 6,803,031 B2 and copending Application No. 10/769,197. Applicants believe that this addresses the Examiner's concerns and respectfully request reconsideration of the application, withdrawal of all rejections, and allowance of the application in view of these actions and remarks.

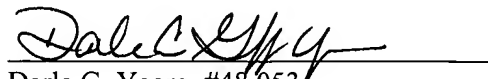
### **Conclusion**

The Applicants appreciate the Examiner's careful and thorough review of the application and submit that the Examiner's concerns have been addressed by the amendments and remarks above. The Applicants accordingly request the Examiner to withdraw all rejections and allow the application. In the event the Examiner believes a telephonic discussion would expedite allowance or help to resolve outstanding issues, prosecution of the application, then the Examiner is invited to call the undersigned at (303) 268-0066.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 19-5117.**

Respectfully submitted,

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